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Abstract: Background: Glycemic variability (GV) is an indicator of glycemic control and can be evaluated by calculating the SD of blood glucose measurements. In humans with diabetes mellitus (DM), adding a glucagon-like peptide-1 (GLP-1) analogue to conventional therapy reduces GV. In diabetic cats, the influence of GLP-1 analogues on GV is unknown. Objective: To evaluate GV in diabetic cats receiving the GLP-1 analogue exenatide extended release (EER) and insulin. Animals: Thirty client-owned cats with newly diagnosed spontaneous DM. Methods: Retrospective study. Blood glucose curves from a recent prospective placebo-controlled clinical trial generated 1, 3, 6, 10, and 16 weeks after starting therapy were retrospectively evaluated for GV. Cats received either EER (200 g/kg) or 0.9% saline SC once weekly, insulin glargine and a low-carbohydrate diet. Mean blood glucose concentrations were calculated and GV was assessed by SD. Data were analyzed using nonparametric tests. Results: In the EER group, GV (mean SD [95% confidence interval]) was lower at weeks 6 (1.69 mmol/L [0.9-2.48]; $P = .02$), 10 (1.14 mmol/L [0.66-1.62]; $P = .002$) and 16 (1.66 mmol/L [1.09-2.23]; $P = .02$) compared to week 1 (4.21 mmol/L [2.48-5.93]) and lower compared to placebo at week 6 (3.29 mmol/L [1.95-4.63]; $P = .04$) and week 10 (4.34 mmol/L [2.43-6.24]; $P < .000$). Cats achieving remission (1.21 mmol/L [0.23-2.19]) had lower GV compared to those without remission (2.96 mmol/L [1.97-3.96]; $P = .01$) at week 6. Conclusions and clinical importance: The combination of EER, insulin, and a low-carbohydrate diet might be advantageous in the treatment of newly diagnosed diabetic cats.

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Glycemic variability in newly diagnosed diabetic cats treated with the glucagon-like peptide-1 analogue exenatide extended release

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Abstract

Background: Glycemic variability (GV) is an indicator of glycemic control and can be evaluated by calculating the SD of blood glucose measurements. In humans with diabetes mellitus (DM), adding a glucagon-like peptide-1 (GLP-1) analogue to conventional therapy reduces GV. In diabetic cats, the influence of GLP-1 analogues on GV is unknown.

Objective: To evaluate GV in diabetic cats receiving the GLP-1 analogue exenatide extended release (EER) and insulin.

Animals: Thirty client-owned cats with newly diagnosed spontaneous DM.

Methods: Retrospective study. Blood glucose curves from a recent prospective placebo-controlled clinical trial generated 1, 3, 6, 10, and 16 weeks after starting therapy were retrospectively evaluated for GV. Cats received either EER (200 µg/kg) or 0.9% saline SC once weekly, insulin glargine and a low-carbohydrate diet. Mean blood glucose concentrations were calculated and GV was assessed by SD. Data were analyzed using nonparametric tests.

Results: In the EER group, GV (mean SD [95% confidence interval]) was lower at weeks 6 (1.69 mmol/L [0.9-2.48]; $P = .02$), 10 (1.14 mmol/L [0.66-1.62]; $P = .002$) and 16 (1.66 mmol/L [1.09-2.23]; $P = .02$) compared to week 1 (4.21 mmol/L [2.48-5.93]) and lower compared to placebo at week 6 (3.29 mmol/L [1.95-4.63]; $P = .04$) and week 10 (4.34 mmol/L [2.43-6.24]; $P < .000$). Cats achieving remission

Abbreviations: DM, diabetes mellitus; EER, exenatide extended release; GLP-1, glucagon-like peptide-1; GV, glycemic variability.

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(1.21 mmol/L [0.23-2.19]) had lower GV compared to those without remission (2.96 mmol/L [1.97-3.96]; $P = .01$) at week 6.

Conclusions and Clinical Importance: The combination of EER, insulin, and a low-carbohydrate diet might be advantageous in the treatment of newly diagnosed diabetic cats.

KEYWORDS

diabetes mellitus, feline, glycemic control, incretin, remission

1 | INTRODUCTION

Glycemic variability (GV) refers to glycemic excursions, including episodes of hypoglycemia and hyperglycemia, during the course of a day or on different days.¹ In humans with diabetes mellitus (DM), GV is an indicator of glycemic control.^{1,2} High GV is considered a risk factor for hypoglycemia, microvascular complications, neuropathy, retinopathy, stroke and all-cause mortality.²⁻⁷ Currently, there is lack of a consensus on the gold-standard method for measuring GV, and several indicators are proposed.^{1,3,4} The SD, which describes the dispersion of values around mean blood glucose, is considered the simplest approach and is commonly used for the evaluation of GV in people.^{3,8}

Incretins such as glucagon-like peptide-1 (GLP-1) are hormones that are released from the gastrointestinal tract during food intake, leading to increased glucose-stimulated insulin secretion. GLP-1 also inhibits glucagon secretion, slows gastric emptying, and enhances satiety.⁹⁻¹¹ Moreover, it increases the proliferation of pancreatic β -cells and decreases their apoptosis, thereby increasing β -cell mass, in rodent models.¹¹

In humans with type 2 DM, administration of the long-acting GLP-1 analogue exenatide extended release (EER) and metformin significantly improves GV compared to metformin alone.¹² Furthermore, the use of a GLP-1 analogue on a background treatment of metformin and basal insulin therapy might have a greater effect in reducing GV than prandial insulin.¹³

In cats, GV has just started to be explored.¹⁴ GV is higher in diabetic cats experiencing posthypoglycemic hyperglycemia during insulin treatment compared to diabetic cats without posthypoglycemic hyperglycemia. Increased GV in cats with posthypoglycemic hyperglycemia is associated with higher insulin dose, higher serum fructosamine concentrations, and decreased glycemic control.¹⁴

Most cats with DM have type 2-like DM. Therefore, it is hypothesized that incretins could be of similar benefit in the treatment of DM in cats as in that of people.¹⁵ EER enhances insulin secretion in healthy cats and treatment appears to be safe in both healthy and diabetic cats.^{16,17} The use of GLP-1 analogues in diabetic cats has been examined in 2 studies^{17,18} and treatment with exenatide is safe, associated with significant weight loss and a decreased requirement for exogenous insulin.¹⁸ Once-weekly administration of the long-acting EER has beneficial effect on remission and metabolic control (no clinical signs, serum fructosamine concentration between 350 and

450 μ mol/L, blood glucose concentration between 4.4 and 15 mmol/L) in insulin-treated cats with DM.¹⁷

To date, the role of GLP-1 analogues on GV has not been investigated in diabetic cats. The objective of the present study was to evaluate GV in diabetic cats receiving the GLP-1 analogue EER and insulin. We hypothesized that EER would lead to a reduction in GV and that cats achieving remission would have lower GV compared to cats without remission.

2 | MATERIALS AND METHODS

2.1 | Study design

An evaluation of blood glucose curves from a recently published prospective placebo-controlled clinical trial was performed.¹⁷ Cats with newly diagnosed DM admitted from January 2013 to January 2015 to the Clinic for Small Animal Internal Medicine of the University of Zurich and the Department of Veterinary Medical Sciences, University of Bologna were included in the trial. The diagnosis of DM was based on clinical signs (eg, polyuria, polydipsia, weight loss), fasting hyperglycemia, glucosuria, and increased serum fructosamine concentration.^{17,19}

Exclusion criteria were previous treatment with insulin or any other antidiabetic medication for >4 weeks before admission, as well as glucocorticoid and progestagen treatment within 3 months prior to admission. Furthermore, cats with concurrent diseases (eg, renal disease, gastrointestinal disorder, heart disease, other endocrinopathies or neoplasia) were excluded. Cats with ketoacidosis or pancreatitis were included in the study if clinical signs had resolved and their general condition had improved within 48 hours of treatment. All cats were thoroughly evaluated (physical examination, complete blood count, serum chemistry, urinalysis, blood pressure measurement, abdominal and thoracic radiography, abdominal ultrasonography).

The 30 client-owned cats with newly diagnosed spontaneous DM included in the study were alternately assigned to 1 of 2 treatment groups. Fifteen cats were treated with EER (Bydureon; Amylin Pharmaceuticals, San Diego, California; 200 μ g/kg) and 15 cats with 0.33 mL of 0.9% saline (placebo), administered subcutaneously by the owner or a veterinarian, once weekly. Owners were blinded to the treatment group of their cats. Both groups received insulin glargine (Lantus, Sanofi Aventis, Meyrin, Switzerland) twice daily subcutaneously and a low-carbohydrate

diet (DM Purina Veterinary Diets; Medical Solution, Steinhausen, Switzerland). EER was administered for at least 16 weeks. In cases of remission, EER treatment was continued for another 4 weeks after cessation of insulin treatment.

The insulin dose was adjusted based on clinical signs, results of physical examination, blood glucose curves and serum fructosamine concentration. In cats achieving remission, the insulin dose was decreased in increments of 0.5 IU per treatment, once weekly. The last dosage before insulin was discontinued was 0.5 IU once daily, for at least 1 week.¹⁷

Follow-up evaluations were performed 1, 3, 6, 10, and 16 weeks after starting therapy in all cats. For the purpose of the present study, blood glucose curves obtained at these time points were evaluated for GV. Blood glucose curves consisted of capillary glucose values measured every 2 hours for 8-12 hours (with each curve consisting of at least 4 measurements) using the validated portable blood glucose meter (AlphaTRAK, Zoetis, Parsippany, New Jersey).²⁰ Hypoglycemia was defined as a blood glucose concentration ≤ 3.6 mmol/L.¹⁷ Remission was defined as absence of clinical signs of DM and normal blood glucose (4-9 mmol/L) and fructosamine (< 350 μ mol/L) concentrations for at least 4 weeks after cessation of insulin therapy.²¹ Further details regarding the previous study are described elsewhere.¹⁷

2.2 | Statistical analysis

All cats from the previous study¹⁷ were included in this retrospective evaluation of blood glucose curves. GV was evaluated as reported previously.¹⁴ Mean blood glucose concentrations of each blood glucose curve generated during follow-up evaluations were calculated. As a marker for GV, their corresponding SD was calculated. Both mean blood glucose concentrations and SD of each blood glucose curve were compared between treatment groups and between cats achieving or not achieving remission at each time point during follow-up. The latter calculations (remission vs nonremission) were carried out in the whole study population as well as within each treatment group if the number of cases with and without remission was ≥ 5 . In addition, differences in mean blood glucose concentrations and GV between week 1 and follow-up evaluations were calculated within each treatment group and within the group of cats achieving and not achieving remission. Regarding the comparison within the group of cats achieving remission, blood glucose curves obtained during remission were excluded from analysis to avoid any bias on GV, as cats in remission per se are expected to have lower GV. Though excluded from analysis, subsequent blood glucose curves from these cats were evaluated to ensure that cats were still in remission and that the criteria of remission (normal glucose concentrations for at least 4 weeks) were fulfilled.

Distribution of sex and breed, frequency of previous antidiabetic medication or ketoacidosis between the treatment groups were compared using Fisher exact test. Fisher exact test was also used to compare the frequency of hypoglycemic episodes and the rate and onset

of remission.¹⁷ The rate of remission was defined as the number of cats achieving remission within the 16-weeks study period.

Differences for age, body weight and daily insulin dosage were analyzed using the Mann-Whitney *U* test or *t* test.¹⁷ Comparisons between groups were made by means of the Kruskal-Wallis test and the Mann-Whitney *U* test, comparisons within groups with the Wilcoxon paired test. Level of significance was set at $P < .05$. All statistical analyses were performed using 2 commercial statistical programs (IBM SPSS Statistics Version 25.0., Armonk, New York and GraphPad Prism Version 8.2.1, GraphPad Software, La Jolla, California).

3 | RESULTS

3.1 | Animals

The EER group consisted of 12 (80%) domestic short- or longhair and 3 (20%) purebred cats including 2 Maine Coons and 1 Norwegian Forest Cat; 9 (60%) were neutered males, 1 (7%) was an intact male and 5 (33%) were spayed females. Median age was 9.3 years (range, 4.3-14) and median body weight was 5.3 kg (range, 4.4-7.4).¹⁷

The placebo group consisted of 14 (93%) domestic short- or longhair and 1 (7%) purebred (Exotic) cats; 5 (33%) cats were neutered males and 10 (67%) were spayed females. Median age was 10 years (range, 2.6-15) and median body weight was 4.5 kg (range, 2.7-8.3).¹⁷

There were no significant differences between the 2 groups regarding age, body weight, breeds, sex, or frequency of cats with previous ketoacidosis or overall antidiabetic medication. Nine cats had ketoacidosis, which resolved within 1-2 days of treatment (3 in the EER group and 6 in the placebo group; $P = .43$).¹⁷

Before inclusion, 8 (53%) cats in the EER group and 10 (67%) in the placebo group received antidiabetic treatment, respectively ($P = .71$). Sixteen cats received some form of insulin treatment within < 4 weeks before inclusion. Ten cats (6 in EER group and 4 in placebo group) were treated with insulin glargine (Lantus) only and 3 cats (1 in EER group and 2 in placebo group) with lente-type insulin (Caninsulin/Vetinsulin, MSD Merck) only. Two cats (both in placebo group) were treated with a combination of short-acting insulin aspart (NovoRapid, Novo Nordisk Pharma AG) and insulin glargine (Lantus). One cat (EER group) received lente-type insulin (Caninsulin/Vetinsulin) first and insulin glargine (Lantus) afterwards. Furthermore, 1 cat in the placebo group was treated with the sulfonylurea glipizide prior to inclusion and 1 cat in the EER group received only an antidiabetic diet.¹⁷

The median insulin glargine dose administered during the study period did not differ between groups (EER 0.41 IU/kg/day; range, 0.11-0.88; placebo 0.38 IU/kg/day; range, 0.22-1.5; $P = .66$ if phases of remission were excluded; EER 0.36 IU/kg/day; range, 0.07-0.88; placebo 0.33 IU/kg/day; range, 0.13-1.5; $P = .49$ if phases of remission were included).¹⁷ There was also no significant difference in baseline results of CBC, biochemical profile, urinalysis and blood pressure measurement.¹⁷

3.2 | Glycemic variability in treatment groups

Reevaluations were scheduled at 1, 3, 6, 10, and 16 weeks after starting treatment. In total, 132 blood glucose curves were available for comparing treatment groups (64 in the placebo group and 68 in the EER group). In 18 cats (60%) blood glucose curves were available from each reevaluation. In 12 cats (40%; 6 cats in the placebo group and 6 cats in the EER group), the following number of glucose curves were available: in 8 cats 4 curves each, in 2 cats 3 curves each, and in another 2 cats 2 curves each. In the placebo and EER groups, 11 and 7 glucose curves were missing, respectively.

Mean blood glucose concentrations are listed in Table 1. Means (mean [95% confidence interval]) were significantly lower in the EER group than in the placebo group at weeks 6 (EER 5.1 mmol/L [4.22-5.98] vs placebo 12.96 mmol/L [9.09-16.84]; $P < .000$) and 10 (EER 5.96 mmol/L [4.31-7.61] vs placebo 11.67 mmol/L [7.14-16.2]; $P = .002$). In the EER group, 14 of 15 cats (93%) and in the placebo group 12 of 15 cats (80%) had episodes of hypoglycemia based on blood glucose curves. The frequency of hypoglycemic episodes was not different between both groups ($P = .6$).¹⁷ The lowest blood glucose concentrations recorded in the EER group was 1.4 mmol/L and in the placebo group 1.8 mmol/L, respectively.

In the EER group, the SD as a marker for GV (mean SD [95% confidence interval]) was significantly lower at weeks 6 (1.69 mmol/L [0.9-2.48]; $P = .02$), 10 (1.14 mmol/L [0.66-1.62]; $P = .002$) and 16 (1.66 mmol/L [1.09-2.23]; $P = .02$) compared to week 1 (4.21 mmol/L [2.48-5.93]). In the placebo group, there were no significant differences in GV from week 1 to any of the other time points. Comparison of the 2 groups revealed significantly lower GV in the EER group compared to the placebo group at week 6 (EER 1.69 mmol/L [0.9-2.48] vs placebo 3.29 mmol/L [1.95-4.63]; $P = .04$) and week 10 (EER 1.14 mmol/L [0.66-1.62] vs placebo 4.34 mmol/L [2.43-6.24]; $P < .000$) (Figure 1).

3.3 | Glycemic variability in cats with and without remission

To compare cats with and without remission, 7 blood glucose curves (from 5 cats) from the remission group were excluded from further analysis because they were generated during remission. In the EER group, 6 of 15 (40%) cats achieved remission after a median of 11 weeks (range, 10-14), while in the placebo group, 3 of 15 (20%)

cats achieved remission after a median time of 10 weeks (range, 8-10) following initiation of treatment. There was no difference in the rate and time to achieve remission between the EER and placebo group (rate $P = .43$; onset $P = .17$).¹⁷ All 9 cats that achieved remission also stayed in remission during the whole study period of 16 weeks. After the end of the study 4 cats (3 in EER group, 1 in placebo) experienced a relapse after a median of 37 months (range, 4-65 months) after remission-onset. The remaining 5 cats (3 in EER group, 2 in placebo group) stayed in remission for a median of 15 months (range, 7-24) follow-up time.

Results on the mean blood glucose concentrations in cats with and without remission are listed in Tables 2 and 3.

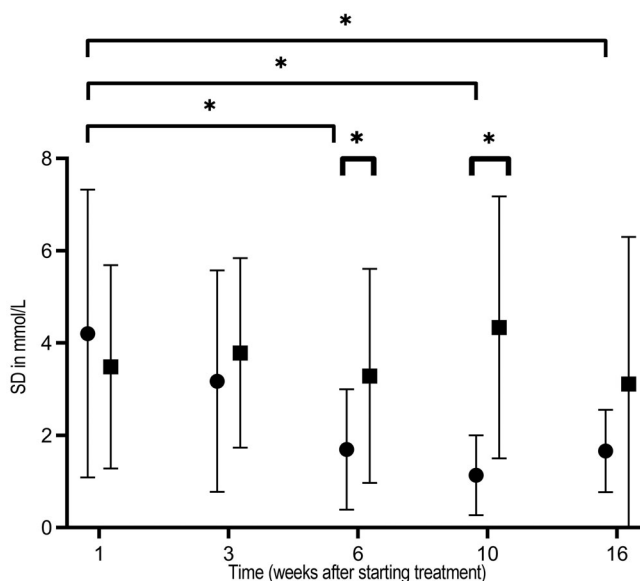


FIGURE 1 Standard deviation as marker for glycemic variability in the exenatide extended release (EER) and in the placebo group. Dots (EER group; $n = 15$) and squares (placebo group; $n = 15$) represent means and bars represent corresponding SDs. Horizontal bars represent significant differences in glycemic variability (GV) between reevaluations and groups. In the EER group, GV is significantly lower at weeks 6, 10, and 16 compared to week 1, whereas no difference was revealed in the placebo group. GV is significantly lower in the EER group compared to the placebo group at weeks 6 and 10. * $P < .05$

TABLE 1 Mean blood glucose concentrations (in mmol/L) in the EER and the placebo group

Reevaluation	EER			Placebo			P
	Mean (mmol/L)	SD (mmol/L)	n	Mean (mmol/L)	SD (mmol/L)	n	
1	16.6	7.7	15	16.1	8.2	13	.77
3	13.4	6.9	13	12.3	7.4	14	.77
6	5.1	1.5	13	13.0	6.7	15	.000
10	6.0	3.0	15	11.7	6.7	11	.002
16	7.0	1.5	12	8.8	4.5	11	.78

Abbreviations: EER, exenatide extended release; n, number of cats.

Within the whole group of cats achieving remission, the SD as a marker for GV was significantly lower at week 6 (1.21 mmol/L [0.23-2.19]) compared to week 1 (3.56 mmol/L [1.77-5.35]; $P = .02$). Within the whole group of cats not achieving remission, no difference in GV was observed between week 1 and any other time point. When cats with and without remission were compared, GV was significantly lower in the remission group at week 6 (remission 1.21 mmol/L [0.23-2.19] vs nonremission 2.96 mmol/L [1.97-3.96]; $P = .01$) (Figure 2).

When only the EER group was evaluated, within cats achieving remission, GV significantly decreased from week 1 (3.67 mmol/L [0.87-6.47]) to week 6 (0.63 mmol/L [0.3-0.95]; $P = .04$). Within the group that did not achieve remission, there was a significant decrease from week 1 (4.56 mmol/L [1.88-7.25]) to week 10 (1.36 mmol/L [0.54-2.17]; $P = .04$). When cats with and without remission from the EER group were compared, GV was significantly lower in the remission group at week 6 (remission 0.63 mmol/L [0.3-0.95] vs nonremission 2.32 mmol/L [1.24-3.4]; $P = .008$) (Figure 3). In the placebo group, the comparison of GV between cats achieving and not achieving remission was not performed due to the limited number of cases (only 3 cats in remission).

4 | DISCUSSION

The present study evaluates GV in diabetic cats receiving the GLP-1 analogue EER once weekly. EER was given in addition to standard treatment consisting of insulin glargine and a low-carbohydrate diet. When compared to values for week 1, GV in the EER group was significantly lower from 6 weeks of therapy until the end of the study at week 16, whereas GV did not change in the placebo group. Comparison between the 2 groups revealed significantly lower GV in the EER group 6 and 10 weeks after initiating therapy.

The importance of GV as a marker for glycemic control in people has increased.^{1,2,4}

Glycated hemoglobin is considered the gold standard for assessing long-term glycemic control in people over time.^{1,4} However, the variable does not take into account short-term fluctuations in blood glucose concentrations which increase the risk for both hypo- and hyperglycemia; moreover, even patients with optimally glycated hemoglobin can have substantial daily fluctuations in blood glucose levels.^{1,2,4,22} Perhaps more importantly, GV, like mean blood glucose, is independently and strongly

predictive of hypoglycemia, while glycated hemoglobin is a poor predictor of hypoglycemic events.²³ Increased GV has several implications for the development of chronic diabetic complications, all-cause mortality and quality of life.^{1,2,4} One important treatment goal in human medicine therefore is to avoid multiple blood glucose fluctuations as they can be even more harmful than stable chronic hyperglycemia.^{1,2}

Currently, there is no gold-standard method for the assessment of GV, and various indices, each with its own advantages and disadvantages, are proposed.^{1,2,4} We used the variable SD in accordance with previous studies of our research group because in human medicine it is widely used and simple to calculate.^{2,8} One limitation of SD is that it implies that measures of glucose concentrations are normally distributed, which is not always the case.^{1,8} However, SD remains a fairly robust measure because a linear relation has been established between the interquartile range and the SD.^{1,2,4} Because of the consistent shape of the glucose distribution in many circumstances, it is often possible to transform the data, so it becomes nearly symmetrical.²⁴ Furthermore, there is a high degree of correlation between SD and other markers for GV²⁵⁻³² and it takes all glycemic oscillations into account. Standard deviation has recently been recommended as a key variable together with the coefficient of variation (SD divided by the mean) in a consensus on continuous glucose monitoring in people.³³

In cats, the concept of GV is not yet well studied. Fluctuations are frequently observed in blood glucose curves in diabetic cats and diabetic cats with posthypoglycemic hyperglycemia have higher GV.¹⁴ In contrast, posthypoglycemic hyperglycemia does not occur in healthy experimental cats treated with insulin, which suggests that they are able to fine-tune glycemia.¹⁴ Good metabolic control is seen in 70% of cats without posthypoglycemic hyperglycemia, but in only 6.7% of cats with this phenomenon.¹⁴ Cats with posthypoglycemic hyperglycemia are considered difficult to control, and in the long-term require continued dose adjustments because of reoccurring hypoglycemic nadirs.³⁴

In the present study, cats in the EER group had lower GV compared to placebo. These findings are in agreement with several human studies, where positive effects of GLP-1 analogues on GV are already known. For example, there is a GV-lowering effect of exenatide in the short-term in human type 2 diabetics.³⁵ Furthermore, exenatide treatment results in greater improvements in GV than does insulin glargine in patients with DM using metformin, a sulfonylurea or both concurrently.^{36,37} In contrast, in human overweight and obese patients

TABLE 2 Mean blood glucose concentrations (in mmol/L) in all cats: comparison between remission and nonremission

Reevaluation	Remission			Nonremission			P
	Mean (mmol/L)	SD (mmol/L)	n	Mean (mmol/L)	SD (mmol/L)	n	
1	14.0	7.8	9	17.6	7.8	19	.27
3	7.8	5.7	8	14.8	6.6	20	.01
6	7.2	6.2	7	9.9	6.3	20	.18
10	5.9	2.7	6	9.7	6.1	18	.08
16	6.2	0.0	1	8.5	3.8	16	.39

Abbreviation: n, number of cats.

TABLE 3 Mean blood glucose concentrations (in mmol/L) in the EER group: comparison between remission and nonremission

Reevaluation	Remission			Nonremission			P
	Mean (mmol/L)	SD (mmol/L)	n	Mean (mmol/L)	SD (mmol/L)	n	
1	14.3	8.8	6	18.2	7.1	9	.29
3	8.3	7.5	5	16.5	4.5	8	.06
6	4.5	1.2	5	5.5	1.5	8	.31
10	4.5	0.9	4	6.7	3.7	9	.17
16	6.2	0.0	1	7.3	1.5	8	.25

Abbreviations: EER, exenatide extended release; n, number of cats.

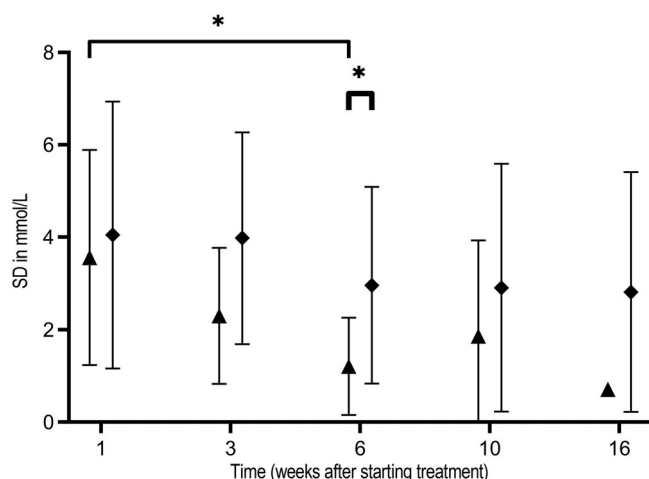


FIGURE 2 Standard deviation as marker for glycemic variability in all cats with and without remission. Triangles (cats with remission; n = 9) and diamonds (cats without remission; n = 21) represent means and bars represent corresponding SDs. Horizontal bars represent significant differences in glycemic variability (GV) between reevaluations and groups. In the remission-group, GV is significantly lower at week 6 compared to week 1, whereas no difference was revealed in the nonremission group. GV is significantly lower in the remission group compared to the nonremission group at week 6. * $P < .05$

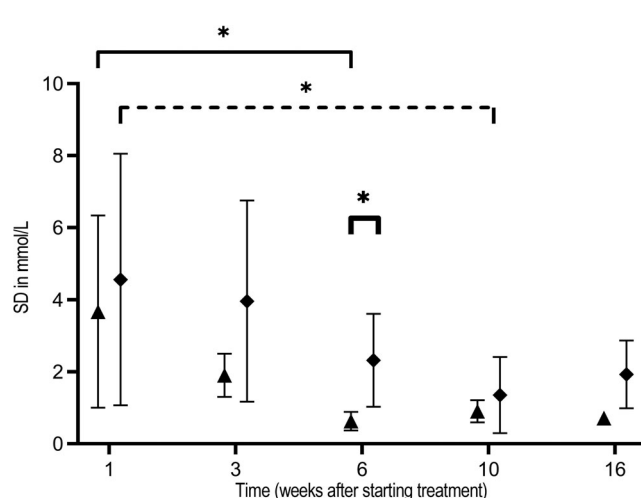


FIGURE 3 Standard deviation as marker for glycemic variability in exenatide extended release group with and without remission. Triangles (cats with remission; n = 6) and diamonds (cats without remission; n = 9) represent means and bars represent corresponding SDs. Horizontal bars represent significant differences in glycemic variability (GV) between reevaluations and groups (continuous line = remission group; interrupted line = nonremission group). In the remission group GV is significantly lower at week 6 compared to week 1. In the nonremission group GV was significantly lower at week 10 compared to week 1. GV is significantly lower in the remission group compared to the non-remission group at week 6. * $P < .05$

inadequately controlled by metformin, there is similar efficacy between exenatide and insulin glargine in terms of GV, but exenatide has a greater effect on body weight and body mass index.³⁸

The improvement of GV in EER-treated cats could be explained by the physiologic effects of GLP-1, especially the glucose-dependent stimulation of insulin secretion and concomitant suppression of glucagon.^{11,35} By enhancing insulin production and secretion after a meal, incretin hormones serve to suppress postprandial hyperglycemia³⁹ and therefore glycemic fluctuations. Furthermore, GLP-1 analogues lead to decelerated gastric emptying, which further attenuates increases in meal-associated blood glucose concentrations.¹¹

In the whole population of cats, GV was lower at week 6 compared to week 1 only in the group that achieved remission, whereas it did not change in the nonremission group. When the 2 groups were compared, GV was significantly lower in those achieving remission 6 weeks after initiating therapy.

In cats with posthypoglycemic hyperglycemia, only 10% of cats achieve remission compared to almost 66% without it.¹⁴ Furthermore, there is less day-to-day variability in blood glucose concentrations in diabetic cats with good glycemic control compared to cats with moderate or poor control.⁴⁰ GLP-1 analogues in diabetic cats slightly improve remission rates.^{17,18} In newly diagnosed and drug-naïve human type 2 DM patients who achieve glycemic remission, sequential treatment with exenatide for 12 weeks induces significantly higher maintenance of 1- and 2-year glycemic remission rates as compared to short-term intensive insulin therapy alone. This effect is no longer apparent after cessation of exenatide.⁴¹

It is likely that diabetic remission in cats occurs through reversal of glucotoxicity and that effective control of hyperglycemia in diabetic patients decreases the deleterious effects of glucotoxicity on

pancreatic β -cells and increases the chance of remission.^{9,42} After rapid recovery from glucotoxicity through insulin glargine, EER might further improve and maintain β -cell function and reverse subsequent insulin-resistance. Results of the present and previous studies^{14,40} suggest that lowering GV should be a preferential goal in the treatment of diabetic cats in order to increase the likelihood of remission. To date, there is no single diagnostic test or cat characteristic identified that reliably predicts remission in diabetic cats at the time of diagnosis.⁴² Although further studies are needed, results of the present study could provide useful information to answer the question as to whether GV could be a potential predictor of remission in diabetic cats.

In the current study, GV was significantly lower in the EER group compared to placebo at weeks 6 and 10.

This exposure time might be needed to reverse glucotoxicity. In human type 2 DM patients, β -cell function normalizes after an 8-week-course of dietary energy restriction.⁴³ Furthermore, in humans with type 2 DM, partial restoration of β -cell function is achieved after 4 weeks of near-normalization of plasma glucose concentrations.⁴⁴

In addition to GV, mean blood glucose values at certain time points were significantly lower in cats in the EER group compared to placebo as well as in cats with remission compared to cats without remission. It is important to note that the number of hypoglycemic events did not differ between groups.¹⁷ This is in line with previous studies on GLP-1 analogues in healthy and diabetic cats.^{18,45} In people and experimental animals, exenatide ceases to stimulate insulin secretion once euglycemia is restored.^{46,47} Furthermore, GLP-1 analogues also suppress glucagon secretion in a glucose-dependent manner,¹¹ which together could be a possible explanation for the low risk of hypoglycemia in GLP-1 treated cats. In contrast to the results of our study, there are no differences in mean blood glucose between the treatment group compared to placebo in a previous study.¹⁸ However, the results of the 2 studies cannot be directly compared because the present study used once-weekly EER and the previous examined effects of the short-acting exenatide with twice daily injections. Furthermore, with only 8 cats and 6 weeks of treatment in the latter study, the power and time span could have been too small to detect differences.

Long-term GLP-1 analogues have become widely used in human medicine. In diabetic cats, the safety of the long-acting EER has already been assessed.¹⁷ Recently, a GLP-1 analogue suitable for once-monthly administration in the cat was presented.⁴⁸ We believe that once-weekly or even once-monthly injections would be convenient additional treatment options in diabetic cats.

When discussing the results of the present study, some limitations need to be considered. First, a relatively small number of cats were evaluated. We consider this study an important starting point which is intended to serve as a basis for further studies on GLP-1 agonists and its potential to reduce GV. Despite the relatively small number of cats, we were able to show significantly lower GV in EER-treated cats and cats with remission compared to placebo and cats without remission, respectively. Furthermore, the number of blood glucose curves was limited, so in some cats, severe blood glucose fluctuations at certain time points after starting therapy might have been

missed. This limitation seems to be of minor relevance because the number of cats with missing blood glucose curves was comparable in both treatment groups. Also, short episodes of hypo- und hyperglycemia might have been missed when using a portable blood glucose meter instead of continuous blood glucose monitoring. Further, the study period was 16 weeks and it is possible that more cats would have achieved remission afterwards. Lastly, GV was evaluated in newly diagnosed diabetic cats without concurrent diseases, so the results of the present study cannot be extrapolated to the general population of diabetic cats and further studies are needed to assess GV in diabetic cats with concurrent diseases.

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CONFLICT OF INTEREST DECLARATION

Eric Zini serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in review of this manuscript.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J*. 2015;39:273-382.
2. Frontoni S, Di Bartolo P, Avogaro A, et al. Glucose variability: an emerging target for the treatment of diabetes mellitus. *Diabetes Res Clin Pract*. 2013;102:86-95.
3. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA*. 2006;295(14):1707-1708.
4. Umpierrez GE, Kovatchev BP. Glycemic variability: how to measure and its clinical implication for type 2 diabetes. *Am J Med Sci*. 2018;356(6):518-527.
5. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, for the DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial—revisited. *Diabetes*. 2008;57(4):995-1001.
6. Zinman B, Marso SP, Christiansen E, et al. Day-to-day fasting glycemic variability in DEVOTE: associations with severe hypoglycemia and cardiovascular outcomes (DEVOTE 2). *Diabetologia*. 2018;61:48-57.

7. Lin CC, Yang CP, Li CI, et al. Visit-to-visit variability of fasting plasma glucose as a predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan diabetes study. *BMC Med*. 2014;26:165.
8. Service FJ. Glucose variability. *Diabetes*. 2013;62(5):1398-1404.
9. Reusch CE. Feline diabetes mellitus. In: Feldman EC, Nelson RW, Reusch CE, Scott-Moncrieff JC, eds. *Textbook of Canine and Feline Endocrinology*. 4th ed. St. Louis, MO: Saunders; 2015:258-314.
10. Gilor C, Graves TK, Gilor S, Ridge TK, Rick M. The GLP-1 mimetic exenatide potentiates insulin secretion in healthy cats. *Domest Anim Endocrinol*. 2011;41:42-49.
11. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
12. Frias JP, Nakhle S, Ruggles JA, et al. Exenatide once weekly improved 24-hour glucose control and reduced glycemic variability in metformin-treated patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2016;19:40-48.
13. FLAT-SUGAR Trial Investigators. Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. *Diabetes Care*. 2016;39(6):973-981.
14. Zini E, Salesov E, Dupont P, et al. Glucose concentrations after insulin-induced hypoglycemia and glycemic variability in healthy and diabetic cats. *J Vet Intern Med*. 2018;32(3):978-985.
15. Reusch CE, Padrucci I. New incretin hormonal therapies in humans relevant to diabetic cats. *Vet Clin N Am Small Anim Pract*. 2013;35:211-224.
16. Padrucci I, Lutz TA, Reusch CE, Zini E. Effects of the glucagon-like peptide-1 (GLP-1) analogues exenatide, exenatide extended-release, and of the dipeptidylpeptidase-4 (DPP-4) inhibitor sitagliptin on glucose metabolism in healthy cats. *Res Vet Sci*. 2015;99:23-29.
17. Riederer A, Zini E, Salesov E, et al. Effect of the glucagon-like peptide-1 analogue exenatide extended release in cats with newly diagnosed diabetes mellitus. *J Vet Intern Med*. 2016;30(1):92-100.
18. Scuder MA, Ribeira Petito M, Unniapan S, et al. Safety and efficacy assessment of a GLP-1 mimetic: insulin glargine combination for treatment of feline diabetes mellitus. *Domest Anim Endocrinol*. 2018;65:80-89.
19. Tschuor F, Zini E, Schellenberg S, et al. Remission of diabetes mellitus in cats cannot be predicted by the arginine stimulation test. *J Vet Intern Med*. 2011;25:83-89.
20. Zini E, Moretti S, Tschuor F, et al. Evaluation of a new portable glucose meter designed for the use in cats. *Schweiz Arch Tierheilkd*. 2009;15:448-451.
21. Sieber-Ruckstuhl NS, Kley S, Tschuor F, et al. Remission of diabetes mellitus in cats with diabetic ketoacidosis. *J Vet Intern Med*. 2008;22:1326-1332.
22. Chon S, Lee YJ, Fraterrigo G, et al. Evaluation of glycemic variability in well-controlled type 2 diabetes mellitus. *Diabetes Technol Ther*. 2013;15:455-460.
23. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. *Diabetologia*. 2007;50:2553-2561.
24. Rodbard D. Optimizing display, analysis, interpretation and utility of self-monitoring of blood glucose (SMBG) data for management of patients with diabetes. *J Diabetes Sci Technol*. 2007;1:62-71.
25. Rodbard D. Glycemic variability: measurement and utility in clinical medicine and research -one viewpoint. *Diabetes Technol Ther*. 2011;13(11):1077-1080.
26. Jung HS. Clinical implications of glucose variability: chronic complications of diabetes. *Endocrinol Metab (Seoul)*. 2015;30(2):167-174.
27. Borg R, Kuenen JC, Carstensen B, et al. ADAG study group: HbA_{1c} and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-derived average glucose (ADAG) study. *Diabetologia*. 2011;54:69-72.
28. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther*. 2009;11(suppl 1):S55-S57.
29. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11:551-565.
30. Rodbard D, Bailey T, Jovanovic L, Zisser H, Kaplan R, Garg SK. Improved quality of glycemic control and reduced glycemic variability with use of continuous glucose monitoring. *Diabetes Technol Ther*. 2009;11:717-723.
31. Rodbard D, Jovanovic L, Garg S. Responses to continuous glucose monitoring in subjects with type 1 diabetes using continuous subcutaneous insulin infusion or multiple daily injections. *Diabetes Technol Ther*. 2009;11:757-765.
32. Baghurst PA. Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm. *Diabetes Technol Ther*. 2011;13:296-302.
33. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631-1640.
34. Roomp K, Rand J. Rebound hyperglycemia in diabetic cats. *J Feline Med Surg*. 2016;18(8):587-596.
35. Irace C, Fiorentino R, Carallo C, Scavelli F, Gnasso A. Exenatide improves glycemic variability assessed by continuous glucose monitoring in subjects with type 2 diabetes. *Diabetes Technol Ther*. 2011;13(12):1261-1263.
36. Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, 2-period, crossover noninferiority trial. *Clin Ther*. 2007;29(11):2333-2348.
37. McCall AL, Cox DJ, Brodows R, et al. Reduced daily risk of glycemic variability: comparison of exenatide with insulin glargine. *Diabetes Technol Ther*. 2009;11(6):339-344.
38. Yin TT, Bi Y, Shen SM, et al. Comparison of glycemic variability in Chinese T2DM patients treated with exenatide or insulin glargine: a randomized controlled trial. *Diabetes Ther*. 2018;9(3):1253-1267.
39. Seyfert TM, Brunner JD, Maxwell LK, et al. Effects of a glucagon-like peptide-1 mimetic (exenatide) in healthy cats. *Int J Appl Res Vet Med*. 2012;10(2):147-156.
40. Alt N, Kley S, Haessig M, Reusch CE. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc*. 2007;230(7):1011-1017.
41. Shi X, Shi Y, Chen N, et al. Effect of exenatide after short-time intensive insulin therapy on glycaemic remission maintenance in type 2 diabetes patients: a randomized controlled trial. *Sci Rep*. 2017;7(1):2383.
42. Gostelow R, Foracada Y, Graves T, et al. Systematic review of feline diabetic remission: separating fact from opinion. *Vet J*. 2014;202(2):208-221.
43. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011;54(10):2506-2514.
44. Højberg PV, Vilsbøll T, Rabøl R, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia*. 2009;52(2):199-207.
45. Rudinsky AJ, Adin CA, Borin-Crivellenti S, Rajala-Schultz P, Hall MJ, Gilor C. Pharmacology of the glucagon-like peptide-1 analog exenatide extended-release in healthy cats. *Domest Anim Endocrinol*. 2015;51:78-85.
46. Degn KB, Brock B, Juhl CB, et al. Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin

- secretion and counterregulation during hypoglycemia. *Diabetes*. 2004;53(9):2397-2403.
47. Parkes DG, Pittner R, Jodka C, Smith P, Young A. Insulinotropic actions of exendin-4 and glucagon-like peptide-1 in vivo and in vitro. *Metabolism*. 2001;50(5):583-589.
48. Schneider EL, Reid R, Parkes DG, et al. A once-monthly GLP-1 receptor agonist for treatment of diabetic cats. *Domest Anim Endocrinol*. 2019;70:106373.

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